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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/512,019	02/24/2000	Guofan Hong	LEE-109	5712

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	14

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/512,019	HONG ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-13,24-30,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-13,29,30,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of the specification and claims 9, 29, 39 and 40, Paper No. 13, 6/12/2003, is acknowledged. Claims 1-22 are still at issue and are present for examination.

Claims 9-13, 24-30, 39 and 40 are at issue and are present for examination. Applicants' arguments filed on 6/12/2003, Paper No. 13, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 24-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 10.

Specification

The disclosure is objected to because of the following informalities:

Figures 4 through 8 each contain nucleotide sequences that are encompassed by the definitions of nucleotide sequence and thus require a sequence identifier and this sequence identifier should be listed either in the figures themselves or in each description of the figure.

In the first line of the abstract applicants recite "genetical modification". It is believed that "the genetic modification" is more appropriate.

Appropriate correction is required.

It is noted that applicants have not commented in response to the above previous objections to the specification .

It is further noted that applicants "Marked-up Version of the Above Amendments" does not list an amended claim 29, but rather an amended claim 30 and this claim lists the two components of the construct as iii) and iv) rather then as I) and ii).

Information Disclosure Statement

Applicants submission of a 1449 along with the previous Paper No. 13, and applicants statement that this was previously submitted on 2/2/2000, is acknowledged, The references listed on the 1449, VR and WR, page 2, are duplicates of references F and J, IDS Paper No. 7, 5/1/2002, and have also been considered and those references on Paper No. 7 have been initialed.

Claim Objections

Claims 29, 39 and 40 are objected to because of the following informalities:

Claim 40 is dependent on rejected claim 39.

Newly amended claims 29 and 39 each recite "*Bacillus stearothermophilus* **of** *Bacillus caldotenax*" . *This should be amended to "Bacillus stearothermophilus* **or** *Bacillus caldotenax."*

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-13, 29, 30 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-13, 29, 30 and 39 (40 dependent from) are indefinite in that they are confusing and unclear in that the verboseness of the newly amended claims resultes in more confusion then the previous version of the claims.

Claims 29, 30, and 39 remain indefinite in that they are confusing in the way in which they are presented. Claims 29, 30, and 39 are each drawn to "a nucleotide sequence encoding a modified DNA polymerase which has an amino acid sequence that shares not less than 95% homology to a DNA polymerase isolated from a strain of *Bacillus stearothermophilus* [of] or *Bacillus caldotenax*, having an amino acid sequence that shares not less than 95% homology to SEQ ID NO: 4, which nucleotide sequence encodes a threonine, proline and leucine at positions 342-344 and a tyrosine at position 422..." It is suggested that an amendment such as "a nucleotide sequence encoding a modified DNA polymerase which has an amino acid sequence that shares not less than 95% homology to [a DNA polymerase isolated from a strain of *Bacillus stearothermophilus* [of] or *Bacillus caldotenax*, having an amino acid sequence that shares not less than 95% homology to] SEQ ID NO: 4, [which] wherein said nucleotide sequence encodes a threonine, proline and leucine at positions corresponding to positions 342-344 and a tyrosine at a position corresponding to position 422..." would

make the claim clearer without limiting the claimed genus. This is how the claim is interpreted for the purpose of advancing prosecution.

Claim 9 (10-13 dependent on) is indefinite in that it is unclear in the recitation "has leucine, glutamate and glutamate residues at positions 342-344, respectively and a phenylalanine at position 422,,," is unclear. It is suggested that applicants amend claim 9 such as "has leucine, glutamate and glutamate residues at positions **corresponding to positions** 342-344, respectively and a phenylalanine at **a position corresponding to** position 422..." as well as amending the parts of each of the claims that recite the specific changes made using the above "corresponding to positions"-type language. For the purpose of advancing prosecution this is how the claim is interpreted.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 10 and 13 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA construct comprising a nucleotide sequence and a host cell comprising said nucleotide sequence, wherein said nucleotide sequence encodes a modified DNA polymerase which during a DNA sequencing reaction has a reduced selective discrimination against the incorporation of the fluorescent dye-labeled dideoxynucleotide terminators ddCTP and ddATP, relative to the fluorescent dye-labeled dideoxynucleotide terminators ddTTP and ddGTP, and

wherein said modified DNA polymerase comprises the amino acid sequence of SEQ ID NO: 4, does not reasonably provide enablement for any nucleotide sequence and a host cell comprising said nucleotide sequence, wherein said nucleotide sequence encodes any modified DNA polymerase which during a DNA sequencing reaction has a reduced selective discrimination against the incorporation of the fluorescent dye-labeled dideoxynucleotide terminators ddCTP and ddATP, relative to the fluorescent dye-labeled dideoxynucleotide terminators ddTTP and ddGTP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was made in the previous office action. In response to this office action applicants have amended claim 9 such that the modified DNA polymerase produced by the claimed host cell has an amino acid sequence that shares not less than 95% homology to SEQ ID NO: 4. Applicants further have stated that by such an amendment, they believe that they have addressed the previous concerns as stated.

This is not found persuasive, because while it is admitted that applicants have amended claim 9 and hence claims 10 and 13, such that the genus of host cells claimed must express a modified DNA polymerase having an amino acid sequence that shares not less than 95% homology to SEQ ID NO: 4, applicants have not limited the claimed genus such that one of skill in the art would know how to make the majority of those host cells encompassed by the rejected claims.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cells producing

modified DNA polymerases broadly encompassed by the claims, including any host cell which produces any DNA polymerase with the specified functional limitations and having 95% homology to the amino acid sequence of SEQ ID NO: 4. While applicants have amended the claimed genus such that it now requires that claimed modified DNA polymerase have at least 95% homology to SEQ ID NO: 4, the only taught representative species of the claimed genus, applicants have not limited the claimed genus to the taught modification of the parent DNA polymerase, which is the essence of applicants invention. Thus the genus that the rejected claims encompasses continues to include any modification of the parent DNA polymerase that results in the claimed functional limitation, provided that the modified DNA polymerase has an amino acid sequence that has at least 95% homology to SEQ ID NO: 4. As previously stated, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that modified DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 4 and the specific mutations that resulted in said DNA polymerase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the

instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA polymerase with the defined functional characteristics because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the specified DNA polymerase function; (B) the general tolerance of DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the specified DNA polymerase functions claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of

those polypeptides of the claimed genus having the specified DNA polymerase characteristics.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any DNA polymerase, provided that the modified DNA polymerase has at least 95% homology to SEQ ID NO: 4, that results in the specified functional characteristics. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

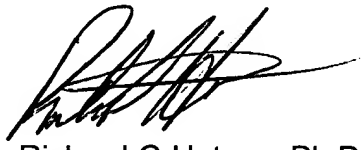
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh